

Diagnosing Cancer

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Tissue (biopsy) is required for diagnosis for every cancer except hepatocellular carcinoma. **Biopsy** is both necessary and the best test. This is true for several reasons. The treatment threshold for drugs that kill healthy tissue and could kill the patient is very high—you better be damn sure it's cancer to give chemo, or remove an organ. The other reason for the biopsy requirement is because “cancer” isn't a diagnosis. “Breast cancer” isn't a diagnosis. “Invasive ductal adenocarcinoma of the breast” isn't a diagnosis. “Invasive ductal adenocarcinoma of the breast ER/PR+ HER2/neu- moderate grade dysplasia stage IIIb (T₂N₃M₀)” is a diagnosis. In addition to confirming the presence of malignancy, a biopsy allows the pathologist to **stain and characterize the cancer**.

At the simplest, we want to be able to **grade** the tumor. The grade comes from the biopsy. But most importantly we can use **immunohistochemistry** to get an idea of what the cancer is doing, see which proteins it's expressing, and obtain targets for directed molecular therapy. A biopsy confirms the diagnosis, assesses the grade, characterizes the specific features of THIS cancer, **but it doesn't stage the cancer**.

Methods to “get tissue” vary. For example, a malignant pleural effusion can be tapped (thoracentesis), a thyroid nodule can undergo a fine-needle aspiration, and a skin lesion can have an excisional biopsy, while a lung cancer might get a bronchoscopy (if central), a CT-guided needle biopsy (if peripheral), or even a complete lobectomy. At this point in one's medical training, knowing “get a biopsy” is sufficient.

Immunohistochemistry / Molecular Testing

Immunohistochemistry means **stains** and **molecular tags**. What the pathologist can do is take multiple slices from a biopsy, stain them, tag them, or use any of the techniques we describe in Genetics #8 *Genetics Testing* to find out what the cell is doing. Not only can it **confirm the diagnosis** by staining positive for markers that are unique to a given cell type or malignancy, but it can also assess for **expression of specific molecular targets**.

Determining which chemotherapy to use is dependent on so many factors that the test will not ask you to select a regimen. You will, however, be asked to identify specific drugs used as molecular targets. Feel that if a patient has invasive ductal adenocarcinoma of the breast with PR+/ER+ but HER2/neu- (even if you don't know what that means yet, keep reading anyway), medications that target PR and ER will help (because the cancer is positive for PR and ER) while drugs that target HER2/neu won't help (because the cancer is negative for HER2/neu. And why this discussion is in this section is because a patient's ER/PR status and HER2/neu status are discovered with molecular testing and special stains.

High-Yield Examples		
Cancer	Sample Test	If Positive, It Means
Breast	ER/PR	Tx: SERMs or aromatase-i
	HER2/neu	Tx: Trastuzumab
ALL	CD10 (flow cytometry)	Dx: CD10 is <u>cALLa</u>
CML	BCR-ABL (FISH)	Tx: Imatinib (RTK-inhibitor)
"Lymphoma"	CD15/30	Dx: Hodgkin's lymphoma
	CD3	Dx: T cell
	CD20	Dx: B cell

Table 11.1: Molecular Testing

High-yield examples worth committing to memory.

Grading Cancer

Grade has limited prognostic value and generally takes a backseat to stage. However, grading still has its uses. Grading combines both mitotic activity and degree of anaplasia. To get a sense of both, a pathologist looks at a slide under a microscope.

Anaplasia is a measure of how undifferentiated the cells in the slide look. A cancer cell comes from a tissue, a differentiated cell in a committed tissue. The cell is more anaplastic the less it looks like the tissue it came from, the more it de-differentiated from the tissue it came from. Anaplastic, undifferentiated, and my conceptualization "de-differentiated" all means the same thing. The more severe the anaplasia, the less like any tissue the cancer cells look, the harder it is to treat.

Mitotic activity determines how rapidly the cells are proliferating. **Aggressive** tumors grow quickly, but are therefore also more susceptible to chemotherapy. **Indolent** tumors are harder to treat because they are not mitotic, but since their doubling time is so long, they also don't kill the host for a long time.

Well-differentiated + Indolent tumors are "good," and are said to be low-grade. **Anaplastic + Aggressive** tumors are "bad," and are called high-grade. Higher-grade tumors generally have a poorer prognosis than low-grade tumors, though grade is not as useful as stage in determining overall prognosis.

Staging Cancer

The test will NOT require interpretation of the stage of a cancer. Do NOT learn the staging protocols for any cancer. Do NOT learn treatment for any cancer based on stage. Just have a general sense of what it means for prognosis and disease burden. Staging describes the degree of **localization or spread** relative to the primary tumor. It describes **size and invasion, nodal involvement, and distant metastasis**, and is called the TNM(S) system. Prognosis is more than just staging. But learning the gestalt early in one's career keeps things in perspective: Stage 1 is good and always curable with surgery, Stage 4 is bad and always fatal.

TNM		I-IV		
T	Tumor size / invasion	Stage 1	Confined to basement membrane	Surgery curative
N	Nodes involved	Stage 2	Through BM but no nodes	Good chance of remission
M	Metastatic sites	Stage 3	Through BM and into nodes	Poor chance of remission
T, N, and M have variable prognostic indications which change from cancer to cancer.		Stage 4	Distant mets	Chemo but no remission

Table 11.2: Staging Cancer

The translation of TNM to stage is beyond the scope of a medical student, except that M > 0 is metastatic (Stage 4). A common pitfall for learners is that the TNM staging system is used to compare cancers of different origins—the prognostic value of the TNM staging can only be applied between cancers of similar origins. For example, colon cancer T₁N₂M₀ and lung cancer T₁N₂M₀ have different prognostic consequences, despite both being T₁N₂M₀.

Diagnosis and **grading** come from the **biopsy**. **Staging** is performed with **imaging**. The simplest conceptual approach is to “look everywhere”—CT scan of the entire body. But staging is far more complex, and there are other more-sophisticated imaging techniques (PET-CT), and certain cancers requires specific interventions (sentinel node injection and retrieval). Regardless, staging requires more than just a microscopic section of the tumor.

Tumor Markers Are NOT FOR DIAGNOSIS

Some cancers make proteins. Those proteins can sometimes be detected in blood. Consider any serologic marker to be **entirely nonspecific**. Which means that **using serum markers to diagnose cancer is always wrong** (except for hepatocellular carcinoma, which does not require a biopsy). Tumor markers also have no prognostic value—**how high a tumor marker is does not predict survival**, remission, or treatment failure. Tumor markers are such poor diagnostic and prognostic tools that their presence or absence will never dictate a change in management. They are **almost useless**.

Never choose a tumor marker as a diagnostic step. **HOWEVER, definitely DO memorize** serum markers and the one or two cancers they correspond to. Tumor markers—values of protein levels in the blood—are useful for **tracking remission and relapse**. They are **NEVER** diagnostic.

Consider this example. A man comes in with prostate cancer, **diagnosed by biopsy**. As part of the workup, he is revealed to have no metastatic lesions but a Prostate-Specific Antigen (PSA) of 5,000. He has his prostate removed—all the healthy cells of the prostate are removed along with the cancerous prostate cells. His healthy prostate cells could make PSA or his prostate cancer cells could make PSA. But since healthy prostate cells don't leave the prostate and cancerous cell can, and since his healthy prostate was removed, if ever PSA were produced in this man, it would be an indication that the cancer cells were left behind or metastasized.

The fact that his PSA was 5,000 altered neither the diagnostic workup nor the treatment—removal of the prostate was determined by a biopsy and staging workup with imaging. After the surgery, his PSA is 0. Which makes sense—his prostate cancer and his prostate were removed. Over the next 12 months his PSA remains 0—confirming remission. In month 13 his PSA rises to 5, signifying that some tissue is expressing PSA. Since his normal healthy prostate was removed, the only tissue that could be making that PSA is prostate-based, identifying that his malignancy is back; he is in relapse, and we go looking.

Serologic Test	Cancer it can be used to track
AFP	Hepatocellular carcinoma, nonseminoma testicular
β -hCG	Choriocarcinoma, trophoblastic disease
Calcitonin	Medullary thyroid
CEA	"Carcinoma," though usually colon
CA-125	Ovarian
CA 19-9	Pancreas
PSA	Prostate

Table 11.3: Tumor Markers Track Disease

Learn the key serologic tests and which cancers they can be used to track remission and relapse for. Never choose these as a diagnostic step.